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EXAMINER
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KUBELIK, ANNE R

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1638

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

10/782,570

Applicant(s)

CAROZZI ET AL.

Examiner

Anne R. Kubelik

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 25 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-11, 19 and 22-26 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-11, 19 and 22-26 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 October 2007 has been entered.
2. Claims 1-11, 19 and 22-26 are pending.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Claim Rejections - 35 USC § 112***

4. Claims 1-11, 19 and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding SEQ ID NO:2 or 4, host cells, plants, plant cells and seeds comprising them, and method of using them to make SEQ ID NO:2 or 4, does not reasonably provide enablement for nucleic acids encoding pesticidal protein with 95% or 90% identity to SEQ ID NO:2 or 4, nucleic acids with 95% or 90% identity to SEQ ID NO:1 or 3, host cells, plants, plant cells and seeds comprising them, and method of using them to make a pesticidal protein with 95% or 90% identity to SEQ ID NO:2 or 4 and a pesticidal protein encoded by a nucleic acid with 95% or 90% identity to SEQ ID NO:1 or 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

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The rejection is modified from the rejection set forth in the Office action mailed 6 February 2007. Applicant's arguments filed 25 October 2007 have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids encoding a pesticidal protein with 95% or 90% identity to SEQ ID NO:2 or 4, nucleic acids with 95% or 90% identity to SEQ ID NO:1 or 3, host cells, plants, plant cells and seeds comprising them, and method of using them to make a pesticidal protein with 95% or 90% identity to SEQ ID NO:2 or 4 and a pesticidal protein encoded by a nucleic acid with 95% or 90% identity to SEQ ID NO:1 or 3.

The instant specification, however, only discusses sequencing of DNAs from non-publicly available bacterial strain ATX13026 (examples 1-4), identification of a nucleic acid, SEQ ID NO:1, that encodes a protein, SEQ ID NO:2, with a low percent identity to delta endotoxins and of a possible start site variant SEQ ID NO:3, which encodes SEQ ID NO:4; the proteins have 27% identity to cry4Aa (examples 5-6), assay of the protein for pesticidal activity against *Lygus lineolaris* (tarnished plant bug) (examples 7-10), and prophetic guidance for expression in plants (examples 11-13).

The instant specification fails to provide guidance for how to make the full scope of nucleic acids encoding pesticidal protein with 95% or 90% identity to SEQ ID NO:2 or 4 and nucleic acids with 95% or 90% identity to SEQ ID NO:1 or 3.

Nucleic acids encoding proteins with 90% identity to the 744 amino acid long SEQ ID NO:2 would encode proteins with 74 amino acid substitutions, and nucleic acids encoding proteins with 90% identity to the 694 amino acid long SEQ ID NO:4 would encode proteins with

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69 amino acid substitutions. Nucleic acids encoding proteins with 95% identity to SEQ ID NO:2 or 4 would encode proteins with 37 or 29 amino acid substitutions, respectively.

Nucleic acids with 90% identity to a 2235 nucleic acid like that of SEQ ID NO:1 would have 223 nucleotide substitutions, and thus encompass those that encode proteins with 223 amino acid substitutions relative to SEQ ID NO:2; these proteins would have 70% identity to SEQ ID NO:2. Similarly, nucleic acids with 90% identity to a 2085 nucleic acid like that of SEQ ID NO:3 would have 208 nucleotide substitutions, thus encompassing those that encode proteins with 208 amino acid substitutions. Nucleic acids with 95% identity to SEQ ID NO:1 or 3 would have 111 or 104 nucleotide substitutions, respectively and thus encompass those that encode proteins with 111 or 104 amino acid substitutions, respectively.

The instant specification fails to provide sufficient guidance for which amino acids of SEQ ID NO:2 and 4 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain the activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional protein.

The guidance in the specification with respect to making amino acids substitutions in AXMI-007 is as follows:

The specification on pg 12, lines 4-7 suggests that substitutions be made at amino acids that are not essential for biological activity, but does not teach any such amino acids.

The specification teaches the 5 highly conserved regions among endotoxins in AXMI-007 (specification pg 4, lines 5-11); the regions encompass a total of 239 amino acids.

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However, it is noted that the region given as conserved Group 3 is much larger than the group is given in the art. Schnepf et al (1998, Microbiol. Mol. Biol. Rev. 62:775-806) teach that conserved Group 3 spans only a maximum of 58 amino acids (Fig 2), not the 145 amino acids given in pg 4, line 8. Additionally, a comparison of SEQ ID NO:2 with the Block 3 consensus sequence indicates that the block only spans from amino acid 543 to amino acid 590. Thus, the actual number of amino acids encompassed by the 5 conserved blocks is 141 amino acids.

The specification, in the paragraph starting on pg 13, line 1, says:

Amino acid substitutions may be made in nonconserved regions that retain function. In general, such substitutions would not be made for conserved amino acid residues, or for amino acid residues residing within a conserved motif, where such residues are essential for protein activity. Examples of residues that are conserved and that may be essential for protein activity include, for example, residues that are identical between all proteins contained in the alignment of Figures 1A, B, and C. Examples of residues that are conserved but that may allow conservative amino acid substitutions and still retain activity include, for example, residues that have only conservative substitutions between all proteins contained in the alignment of Figures 1A, B, and C. However, one of skill in the art would understand that functional variants may have minor conserved or nonconserved alterations in the conserved residues.

Conservative substitutions are defined on pg 12, lines 11-16. A search of the originally filed Fig. 1, shows that there are 5 positions that are identical among all the proteins in the Figure, and 7 positions that have only conservative substitutions among all proteins.

The specification teaches that there are generally 5 highly conserved regions among delta-endotoxins, and that these have a similar structure (pg 12, lines 20-31).

Thus, the structural guidance in the specification relies on function.

The specification, on pg 11, lines 15-20, states:

Variant proteins encompassed by the present invention are biologically active, that is they continue to possess the desired biological activity of the native protein, that is, retaining pesticidal activity. By "retains activity" is intended that the variant will have at least about 30%, preferably at least about 50%, more preferably at least about 70%, even more preferably at least about 80% of the pesticidal activity of the native protein.

Further, the claims require that the encoded protein have pesticidal activity.

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Pests are described in the specification as including, but “not limited to, insects, fungi, bacteria, nematodes, mites, ticks, and the like”, with particular interest in insect pests “selected from the orders Coleoptera, Diptera, Hymenoptera, Lepidoptera, Mallophaga, Homoptera, Hemiptera, Orthoptera, Thysanoptera, Dermaptera, Isoptera, Anoplura, Siphonaptera, Trichoptera, *etc.*” (pg 30, lines 16-20). Thus, “pests” are not limited to plant pests or to insects.

Thus, there would appear be some conflict between the claims’ recitation of “pesticidal activity”, due to the specification’s very broad definition of “pests”, and the specification’s indication that variant proteins should have the same pesticidal activity as the original protein.

The knowledge in the art is as follows:

No *Bacillus Cry* endotoxin has been identified to date that has toxicity all of pests listed in the specifictaion, and none has toxicity to fungi or bacteria or many of the orders listed (see, for example, Bravo et al, 2005, Comprehensive Molecular Insect Science 6:175-205, paragraph spanning pg 176-177). Additionally, many Cry proteins have toxicity only to insects that are not pests for plants, for example, mosquitoes (Bravo et al, pg 177, right column, paragraph 1). Lastly, each *cry* protein only has activity against one or few insect species (de Maagd et al, 1999, Appl. Environ. Microbiol. 65:4369-4374, see pg 4369, column 1, paragraph 1).

Much is known about the structure of Cry proteins, including a crystal structure shared among proteins with little amino acid sequence similarity (Bravo et al, pg 178, right column, paragraph 2).

However, making amino acid substitutions in *cry* proteins is unpredictable.

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Aaronson et al (2001, FEMS Microbiol. Lett. 195:1-8) teach that there are extensive functional interactions between the three domains of Cry proteins and that more than one domain is involved in toxin specificity and binding (paragraph spanning the columns on pg 7). de Maagd et al (2001, Trends Genet. 17:193-199) teach that domains II and III are involved in insect specificity (pg 194, right column, paragraph 3) and that domains I and II have coevolved towards certain specificities (pg 196, left column, paragraph 2, and pg 197, left column, paragraph 4). Regions involved in insect toxicity in one Cry protein are not involved in others (Bravo et al, pg 187, right column, paragraph 1).

Even conservative substitutions in nonconserved regions can have unexpected effects on protein function (de Maagd et al, 1999, Figs 2 and 3). A single amino acid substitution in a *cry* protein may alter its insecticidal specificity, and toxicity must be determined empirically (Tounsi et al, 2003, J. Appl. Microbiol. 95:23-28; see pg 27, column 2, paragraph 2). De Maagd et al (2001) concludes that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2).

Further, even binary proteins, which require interaction with another Cry protein for function, can have the three-domain structure (Jones et al, FASEB J. 2007 21:4112-4120, see paragraph spanning pg 4117-4118). Thus, while much is known about the structure of Cry proteins, relatively little is known about the structures responsible for function.

Point mutations and substitutions of a few amino acids have been made in Cry proteins; however, no one has substituted up to 223 amino acids of a Cry protein, as encompassed the claimed nucleic acids.



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From the guidance in the specification, it would appear that the vast majority of the amino acids in SEQ ID NO:2 and 4 could be substituted. However, the teachings discussed above indicate that making 223 amino acid substitutions in a *cry* protein would be unpredictable, if it is even possible.

Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteins that have up to 223 random amino acid substitutions to find those that have pesticidal activity would require undue experimentation.

Further, one of skill in the art could not without undue experimentation make a protein with 223 amino acid substitutions and with *L. lineolaris* pesticidal activity.

AXMI-007 has the most similarity to *cry* proteins with toxicity to mosquito (*cry*4Aa, *cry*10Aa and *cry*19Ba; see Ibarra et al, 2003, Appl. Environ. Microbiol. 69:5269-5274; abstract and Table 2). AXMI-007, however, is toxic to the Euhemipteran *L. lineolaris*. Thus, one of skill in the art could not use the limited sequence similarity to *cry*4Aa, *cry*10Aa and *cry*19Ba as guides for making a *L. lineolaris* toxic protein with 223 amino acid substitutions relative to SEQ ID NO:2.

Given the novelty of AXMI-007 and the unpredictability making in amino acid substitutions in *cry* proteins, of one of skill in the art could make a protein with up to 223 amino acid substitutions relative to SEQ ID NO:2, the protein would likely have a very different insect

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toxicity than AXMI-007. The specification does not teach the insect toxicity of such proteins. Many plants transformed with a nucleic acid encoding a protein that has pesticidal activity as defined in the specification would not be resistant to insects that are pests to plants and/or would not have the structure of a Cry protein. Therefore, one would not know how to use nucleic acids encoding proteins with up to 223 amino acid substitutions relative to SEQ ID NO:2.

Thus, extensive teachings are required for making nucleic acids encoding *Cry* proteins with up to 223 amino acid substitutions relative to SEQ ID NO:2 or 4, as encompassed by the claimed nucleic acids. These teachings are not provided for by the specification. The specification also fails to overcome the unpredictability of making large numbers of amino acid substitutions in *Cry* proteins by providing no working examples of proteins with up to 223 amino acid substitutions relative to AXMI-007.

As the specification does not overcome the unpredictability discussed above by describing the transformation of any plant with a pesticidal protein with 95% or 90% identity to SEQ ID NO:2 or 4, nucleic acids with 95% or 90% identity to SEQ ID NO:1 or 3, or a complement of those nucleic acids, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with insect resistance, if such plants are even obtainable.

Given the claim breadth, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

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Applicant urges they do not have to provide support for making a protein with up to 223 amino acid substitutions with no experimentation, only for making it with no undue experimentation (response pg 7).

This is not found persuasive because it would require undue experimentation to make a protein with up to 223 amino acid substitutions, given the insufficient guidance in the specification and the unpredictability of making amino acid substitutions in Cry proteins. The specification must provide sufficient guidance for making a protein with up to 223 amino acid substitutions with no *undue* experimentation, but it does not.

Applicant urges *Wands* does not require a working example of every pesticidal protein that could be used to practice the present invention (response pg 7).

This is not found persuasive. A working example of every pesticidal protein that could be used to practice the present invention is not being required. A teaching of how to make the full scope of claimed nucleic acids that encode pesticidal proteins is required, however. Such a teaching is not provided by the specification.

Applicant urges that sufficient guidance for making and using the recited sequences is present on pg 8-13, the sequences are limited by percent identity and function, Cry proteins are well-known, citing Crickmore, and the necessary techniques are routine (response pg 7-8).

This is not found persuasive. Limiting the percent identity of the claimed nucleic acid and requiring a function do not teach which amino acid substitutions may be made in the proteins. The guidance on pg 8-11 merely discusses fragment size, percent identity, and calculation of percent identity. However, guidance for determining percent identity does not

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teach the necessary and sufficient structural features of the claimed nucleic acids, and does not teach which amino acids could be substitutive with which other amino acids. The guidance on pg 9-13 and examples 7-12 fails to sufficiently teach which amino acid substitutions to make in SEQ ID NO:2, 4 or 6, given the unpredictability in making amino acid substitutions in cry proteins. Methods of assay do not teach which amino acid substitutions to make.

Further, according to the naming system defined by Crickmore, SEQ ID NO:2's less than 28% identity to other Cry proteins places it in a different primary rank and places it in outlying Cry lineages (pg 808, left column, paragraph 2-4; Fig. 1) ; however, its very different insect toxicity suggests the identity relationship is deceptive.

Applicant urges that one would only need to make the claimed variants and assay them for activity using routine methods; given this and the skill of those in the art, the amount of experimentation is not undue (response pg 8)

This is not found persuasive. Making the claimed variants and assaying them for activity would require undue experimentation because the specification does not provide sufficient guidance as to which 223 amino acid substitutions can be made in SEQ ID NO:2. Further, the art teaches the unpredictability of amino acid interactions in cry proteins (Aaronson et al, paragraph spanning the columns on pg 7; de Maagd et al, 1999, pg 4369, column 1, paragraph 1; de Maagd et al, 2001, pg 194, right column, paragraph 3; Bravo et al, pg 187, right column, paragraph 1). Further, no one, even to date, has substituted 223 amino acids in a Cry protein. Thus, one would need to randomly make nucleic acids encoding proteins with 223 amino acid substitutions and test them. Because this would require trial and error experimentation and

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because of the likelihood of protein inactivation (see Guo et al, pg 9209, right column, paragraph 2), this experimentation would be undue.

Applicant urges that in *Genentech* no starting materials were disclosed, while here there is specific sequences and sufficient guidance (response pg 8-9).

This is not found persuasive. The instant rejection is a scope of enablement rejection; the invention is enabled for nucleic acid encoding SEQ ID NO:2. The specification, however, does not provide adequate guidance for making up to 223 amino acid substitutions in SEQ ID NO:2. The art discussed above indicates that even though much is known about Cry protein structure, not enough is known about the structure/function relationship to predict a protein's toxicity.

Applicant urges that *Genentech* states "reasonable detail must be provided in order to enable members of the public to understand and carry out the invention" and *Hybritech* characterizes "undue experimentation" as that in which "there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out" (response pg 9).

This is not found persuasive because *Wands* provides another way to determine if there is undue experimentation. This way not defined by a lack of starting material, but by limitations in the guidance in the specification, the knowledge in the art, and the level of predictability in the art. Additionally, in the instant case, reasonable detail is not provided to enable members of the public to understand and carry out the invention.

Applicant urges the specification provides a starting material and description regarding

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amino acid substitutions, in the form of conserved residues and domains and Fig 1 (response pg 9-10).

This is not found persuasive. Fig. 1 has only 5 positions that are identical among all the proteins in the Figure, and only 7 positions that have only conservative substitutions among all 239 amino acids as given in the specification, and 141 amino acids as those regions are defined in the art. Together, these amino acids total less than 25% of the SEQ ID NO:2's length. The art indicates that more guidance is needed.

The findings and teachings of Aaronson et al, Angsuthanasombat, de Maagd et al, 1999, Bravo et al, Tounsi et al and de Maagd et al, 2001, as well as the references cited by Applicant in the response filed 16 October 2006 (Jenkins, Rajamohan, Lee, Scharzt and Masson) show that interactions between amino acids in Cry proteins is much more complex than can be predicted from guidance suggesting only making conservative substitutions or limiting substitutions to loops. De Maagd et al (2001) specifically teaches that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2).

Applicant urges that *Amgen* supports the enablement of the instant invention because here there is no claim for all analogs; because the claims are limited by percent identity they are drawn to similar analogs, which the Court justified in *Amgen* (response pg 10).

This is not found persuasive. The teachings above indicate that the toxicity of the variants proteins encoded by the claimed nucleic acids is not known, nor can it be predicted. One of skill in the art could not without undue experimentation make a protein with 223 amino acid substitutions and with *L. lineolaris* pesticidal activity.

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*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991) at pg 1028:

Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, **with attendant uncertainty as to what utility will be possessed by these analogs**, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. (*emphasis added*)

Applicant urges Guo's results only suggest that a large number of substitutions were not produced, not that they could not be; the instant specification provides guidance for which amino acids are not likely to tolerate random substitution (response pg 10-11).

This is not found persuasive. Guo's random mutagenesis method allowed substitutions wherever they could occur. Given that the probability that a single random amino acid substitution inactivates an enzyme is 34%, making up to random 223 amino acid substitutions in SEQ ID NO:2 is unlikely to be successful. Further, limiting substitutions only to loops would not allow one to make 223 amino acid substitutions, as there are just not that many amino acids in the loops.

Applicant urges detailed information about Cry secondary and tertiary protein structure was known, citing Li and Morse; they provide guidance for determining regions that would tolerate modification (response pg 11).

This is not found persuasive because general knowledge of Cry secondary and tertiary protein structure does not provide information on which amino acids are critical for toxicity toward *L. lineolaris*, which is the function taught in the specification. Proteins with up to 223 amino acid substitutions relative to SEQ ID NO:2 would likely have a very different insect toxicity than AXMI-007, if such toxins could even be made.

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It is noted that the protein taught by Li et al is a cry3Aa protein, which the instant specification teaches has only 19% identity to SEQ ID NO:2 (Table 1), and that taught by Morse et al is a cry2Aa protein, which presumably has less than 5% identity to SEQ ID NO:2. This is relevant because de Maagd et al, 1999, teach that that the crystal structure of Cry1C only allows for limited prediction of the structure of Cry1Aa (pg 4373, right column, paragraph 4), which by Crickmore's nomenclature system would have between 45% and 78% identity to one another. Thus, the teachings of Li and Morse would have provide only limited guidance to one making 223 amino acid substitutions in SEQ ID NO:2.

Applicant urges that one could choose possible modifications based on the regions conserved among protein family members, then test for pesticidal activity (response pg 11-12).

This is not found persuasive because there are no family members for AXMI-007 (SEQ ID NO:2). The instant Table 1 shows that AXMI-007 has 27% identity to cry4Aa, 25% identity to cry10Aa, and 25% identity to cry19Ba. AXMI-007, however, is toxic to the Euhemipteran *L. lineolaris*. Comparison to cry4Aa, cry10Aa or cry19Ba would not let one know which amino acids are critical for toxicity toward *L. lineolaris*, the function of AXMI-007, as cry4Aa, cry10Aa and cry19Ba are all mosquito toxins.

Applicant urges that the assertion that claims to nucleic acid encoding Cry proteins with a few amino acid substitutions would be enabled acknowledges that one of skill in the art would know how to make and test variant sequences; that guidance and testing would be the same for making and testing up to 223 amino acid substitutions (response pg 12).



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This is not found persuasive. Making a few amino acid substitutions is very different than making 223. The unpredictability both in making that many amino acid substitutions in a protein (see Guo et al, discussed above) indicate that making that many substitutions is very unlikely to be successful. The unpredictability in making amino acid substitutions in Cry proteins (see Aaronson et al, Angsuthanasombat, de Maagd et al, 1999, Bravo et al, Tounsi et al and de Maagd et al, 2001, discussed above) indicate that one could not know what activity the proteins would have, much less *L. lineolaris* toxicity.

5. Claims 1-11, 19 and 22-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action mailed 6 February 2007. Applicant's arguments filed 25 October 2007 have been fully considered but they are not persuasive.

Nucleic acids encoding a pesticidal protein with 95% or 90% identity to SEQ ID NO:2 or 4 and nucleic acids with 95% or 90% identity to SEQ ID NO:1 or 3, wherein the nucleic acid encodes a pesticidal protein are essential to the operation of the claimed invention. As nucleic acids encoding proteins with 95% or 90% identity to SEQ ID NO:2 would encode proteins with 73 amino acid substitutions and nucleic acids with 95% or 90% identity to SEQ ID NO:2 encompass those that encode proteins with 220 amino acid substitutions, the claims are drawn to

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a broad genus of nucleic acids. The level of skill and knowledge in the art at the time of filing was such that no other proteins within the scope of the claims were known. ~~BY EXAMINATION~~

The specification, on pg 11, lines 15-20, states:

Variant proteins encompassed by the present invention are biologically active, that is they continue to possess the desired biological activity of the native protein, that is, retaining pesticidal activity. By "retains activity" is intended that the variant will have at least about 30%, preferably at least about 50%, more preferably at least about 70%, even more preferably at least about 80% of the pesticidal activity of the native protein.

Further, the claims require that the encoded protein have pesticidal activity.

Pests are described in the specification as including, but "not limited to, insects, fungi, bacteria, nematodes, mites, ticks, and the like", with particular interest in insect pests "selected from the orders Coleoptera, Diptera, Hymenoptera, Lepidoptera, Mallophaga, Homoptera, Hemiptera, Orthoptera, Thysanoptera, Dermaptera, Isoptera, Anoplura, Siphonaptera, Trichoptera, *etc.*" (pg 30, lines 16-20). Thus, "pests" are not limited to plant pests or to insects.

Thus, there would appear be some conflict between the claims' recitation of "pesticidal activity", due to the specification's very broad definition of "pests", and the specification's indication that variant proteins should have the same pesticidal activity as the original protein.

At the time of filing it was known that each *cry* protein only has activity against one or few insect species (de Maagd et al, 1999, Appl. Environ. Microbiol. 65:4369-4374, see pg 4369, column 1, paragraph 1).

The specification describes no relevant characteristics or motifs for the claimed nucleic acids or the proteins they encode other than identity to SEQ ID NO:1-4 or structures common to all three-domain Cry proteins.

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Aaronson et al (2001, FEMS Microbiol. Lett. 195:1-8) teach that there are extensive functional interactions between the three domains of Cry proteins and that more than one domain is involved in toxin specificity and binding (paragraph spanning the columns on pg 7). de Maagd et al (2001, Trends Genet. 17:193-199) teach that domains II and III are involved in insect specificity (pg 194, right column, paragraph 3) and that domains I and II have coevolved towards certain specificities (pg 196, left column, paragraph 2, and pg 197, left column, paragraph 4). Regions involved in insect toxicity in one Cry protein are not involved in others (Bravo et al, pg 187, right column, paragraph 1). de Maagd et al (2001) concludes that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2).

Furthermore, the specification does not describe the structures or amino acids required for the biological activity, *L. lineolaris* toxicity, of SEQ ID NO:2 or 4, nor does it describe the structural features that distinguish pesticidal protein-encoding nucleic acids with 95% or 90% identity to SEQ ID NO:1 or 3 from other nucleic acids with 95% or 90% identity to SEQ ID NO:1 or 3 or pesticidal proteins with 95% or 90% identity to SEQ ID NO:2 or 4 from other proteins with 95% or 90% identity to SEQ ID NO:2 or 4.

The only species reduced to practice in the specification is SEQ ID NO:1, which encodes SEQ ID NO:2, and a fragment of SEQ ID NO:1, SEQ ID NO:3, which encodes SEQ ID NO:4. Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, SEQ ID NO:1 and 2 and their fragments are insufficient to describe the claimed genus.

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Hence, Applicant has not, in fact, described nucleic acids encoding a pesticidal protein with 95% or 90% identity to SEQ ID NO:2 or 4 and nucleic acids with 95% or 90% identity to SEQ ID NO:1 or 3, wherein the nucleic acid encodes a pesticidal protein, within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Applicant urges the claims recite percent identity, for which the methods for determining are routine; many Cry proteins are known in the art, as are their structures and functions associated with particular structures, regions and motif, citing pg 2 and 12-13 and the Fig 1 legend (response pg 13-14).

This is not found persuasive because the structures associated with particular the disclosed function, *L. lineolaris* toxicity, are not known in the art or described in the specification.

Applicant urges that it was known that cry proteins have three domains, a helix bundle, a three-sheet domain and a beta sandwich motif, citing Li, providing very specific and definite structural parameters to the claimed sequences (response pg 14).

This is not found persuasive. These general characteristics are true of every Cry protein, including those with toxicity to lepidopterans, coleopterans, nematodes and mosquitoes, those

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that only work when associated with other Cry proteins, and those native proteins that do not appear to have any toxicity at all. These basic structures are merely characteristics of three-domain Cry proteins. They are not specifically associated with the disclosed function, *L. lineolaris* toxicity. de Maagd et al (2001) teaches that the determination of insect specificity of endotoxins is still not understood (pg 198, right column, paragraph 2). Additionally, it is noted that the claims are not limited to nucleic acids encoding Cry proteins.

Applicant urges relevant motifs were known, including the domains and structure taught by Li, and conserved regions taught in the specification (response pg 14).

This is not found persuasive because these structures are common to all three-domain Cry proteins and have no relationship to their insect specificity. The specification does not describe the motifs or amino acids required for *L. lineolaris* toxicity.

Applicant urges individual support for each species is not required; they have provided exemplary nucleotide and amino acid sequences and variants and fragments thereof, and numerous Cry proteins were known in the art, allowing one to envision that claimed invention (response pg 14-15).

This is not found persuasive because those of skill in the art say that the relationship between structure and function is not well-known in Cry proteins. Aaronson et al, de Maagd et al, 1999, Bravo et al, and de Maagd et al, 2001, make it clear that the correlation between that function and a structure is not sufficiently known in cry proteins as a whole, and the specification does not describe the motifs and amino acids required for SEQ ID NO:2 biological activity.

Further, Applicant has not provided variants; all the disclosed nucleic acid sequences are

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SEQ ID NO:1 or a fragment thereof. The “variant” SEQ ID NO:3, which encodes the 694 amino acid long SEQ ID NO:4, is merely a 2085 nucleotide long fragment of the 2235 nucleotide long SEQ ID NO:1, which encodes the 744 amino acid long SEQ ID NO:2.

Applicant urges the recitation of a predictable structure is sufficient to satisfy the written description requirement (response pg 15).

This is not found persuasive because the correlation between structure and function is also required, but not provided by the instant specification. The relationship between structure and specific pesticidal function was not described in the specification.

Applicant urges the claim recite functional characteristics that distinguish the claimed sequences, as well as fragments (response pg 16).

This is not found persuasive. The specification does not describe the structure required for the function, nor does it describe the structural features that distinguish pesticidal protein-encoding nucleic acids with 95% or 90% identity to SEQ ID NO:1 from other nucleic acids with 95% or 90% identity to SEQ ID NO:1 or 3 or pesticidal proteins with 95% or 90% identity to SEQ ID NO:2 from other proteins with 95% or 90% identity to SEQ ID NO:2 or 4. Further, the specification’s definition of pests included bacteria and fungi; the specification describes no structures responsible for that function.

### *Conclusion*

6. No claim is allowed.

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7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

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January 31, 2008



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